Journal of the American College of Cardiology
© 1999 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 33, No. 5, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(98)00694-9

# Effects of Paroxetine Hydrochloride, A Selective Serotonin Reuptake Inhibitor, on Refractory Vasovagal Syncope: A Randomized, Double-blind, Placebo-controlled Study

Enrico Di Girolamo, MD, Cesare Di Iorio, MD,* Panfilo Sabatini, MD,* Luigi Leonzio, MD,* Carmela Barbone, MD, Antonio Barsotti, MD

*Chieti, Italy*

**OBJECTIVES** The purpose of the study was to determine whether the well tolerated serotonin reuptake inhibitor paroxetine hydrochloride could prevent vasovagal syncope in patients resistant to or intolerant of previous traditional therapies.

**BACKGROUND** Serotonergic mechanisms play a major role in the processes leading to neurocardiogenic vasovagal syncope, and serotonin reuptake inhibitors have been reported to be effective in preventing refractory syncope.

**METHODS** Sixty-eight consecutive patients (26 men and 42 women, mean age 44.7 ± 16.5 years) with recurrent syncope and positive head-up tilt test and in whom standard therapies with beta-adrenergic blocking agents, vagolytic, negative inotropic or mineral corticoid agents were ineffectual or poorly tolerated were referred for study. Patients randomly received either paroxetine at 20 mg once a day or a placebo. A head-up tilt test was then reperformed after one month of treatment, and the clinical effect was noted over a mean follow-up of 25.4 ± 7.9 months.

**RESULTS** The response rates (negative tilt test) after one month of treatment were 61.8% versus 38.2% ($p < 0.001$) in the paroxetine and placebo groups, respectively. During follow-up spontaneous syncope was reported in six patients (17.6%) in the paroxetine group as compared to 18 patients (52.9%) in the placebo group ($p < 0.0001$). Only one patient (2.9%) asked to be discontinued from the drug for severe side effects.

**CONCLUSIONS** Paroxetine was found to significantly improve the symptoms of patients with vasovagal syncope unresponsive to or intolerant of traditional medications and was well tolerated by patients. (J Am Coll Cardiol 1999;33:1227–30) © 1999 by the American College of Cardiology

Recurrent syncope is a common clinical problem that lacks adequate treatment. The exact pathophysiologic mechanism of vasovagal syncope remains unclear and represents a fascinating challenge to the clinicians who try to explain why this phenomenon occurs. The introduction of head-up tilt testing almost ten years ago (1) provided a simple laboratory test to evaluate for neurally mediated syncope.

In individuals predisposed to neurocardiogenic syncope, the assumption of a passive upright posture leads to gravitationally mediated venous pooling of blood in the lower extremities. This downward displacement of intravascular volume results in a significant decrease of cardiac output, and arterial baroreceptor reflexes are activated, resulting in a reflex increase in sympathetic stimulation (2–4). The sympathetically mediated increase in contractility in a preload reduced left ventricular cavity (5) is believed to activate unmyelinated vagal C-fibers (ventricular mechanoreceptors). Stimulation of these receptors produces a large afferent signal to the brain stem and inhibition of sympathetic outflow occurs (4–7).

Several neurotransmitters are believed to facilitate vasovagal reactions by inhibiting the neuroadrenergic system. In addition to catecholamines (8,9), opioid peptides (9,10), arginin-vasopressin (11), nitric oxide (11) and adenosine (12), it has been reported that 5-hydroxy-triptamine (serotonin) may play an important role in the modulation of central nervous blood pressure and heart rate regulation thus, fluctuations in central serotonin levels being supposed to facilitate the pathogenesis of neurocardiogenic vasovagal syncope. As reported in experimental models, the sudden sympathetic withdrawal responsible for vasovagal syncope appears quite similar to that produced by the injection of serotonin into the intercerebral ventricular areas (13,14).

From the Cardiovascular Clinic Institute "G. D'Annunzio" University, *Cardiologic Division—C.C.U. "SS. Annunziata" Hospital, Chieti, Italy. Financial support was guaranteed by the Institutional Fund for Clinical Research.

Manuscript received March 24, 1998; revised manuscript received October 27, 1998, accepted December 22, 1998.

**Table 1.** Clinical Characteristics

| Characteristics | Paroxetine | Placebo | p Value |
|---|---|---|---|
| No. of patients | 34 | 34 | |
| Age (yr) | 43.2 ± 16.4 | 46.1 ± 13.5 | 0.429 |
| Gender (M/F) | 12/22 | 14/20 | 0.071 |
| Syncopes/yr | 7.2 ± 2.1 | 8.1 ± 3.4 | 0.194 |
| Duration of history (years) | 3.8 ± 0.9 | 4.2 ± 1.3 | 0.145 |
| Systolic blood pressure (mm Hg) | 119.7 ± 17.2 | 121.4 ± 16.8 | 0.681 |
| Diastolic blood pressure (mm Hg) | 72.4 ± 11.5 | 75.1 ± 12.1 | 0.349 |
| Heart rate (beats/min) | 76.2 ± 14.3 | 79.2 ± 11.7 | 0.347 |
| Mean positive time (min) | 31.4 ± 11.2 | 29.2 ± 9.7 | 0.390 |

Several studies have been undertaken to evaluate the efficacy of pharmacotherapy on vasovagal syncope, but a real gold standard of tilt-guided therapy has not been established yet.

Selective serotonin reuptake inhibition by fluoxetine or sertraline has been reported to be effective in patients with refractory vasovagal syncope, but these trials have not been placebo-controlled (15–17). Thus, to determine whether the new, well-tolerated, serotonin reuptake inhibitor paroxetine would have similar effects in patients with refractory vasovagal syncope and positive head-up tilt table test, the following randomized, double-blind, placebo-controlled study was undertaken.

## METHODS

**Study population.** Sixty-eight consecutive patients (26 men and 42 women, mean age 44.7 ± 16.5 years) with refractory syncope and nitrate-potentiated tilt test were referred for study. Etiology of syncope remained unexplained despite a complete history and physical examination which included: cardiologic and neurologic assessment, computed axial tomography or magnetic resonance of the brain, neck vessel Doppler flowmeter, carotid sinus massage and blood pressure determination (both supine and orthostatic), 12-lead electrocardiogram, chest X-ray, routine laboratory tests, two dimensional echocardiography and 24-h Holter monitoring and exercise stress test. Electrophysiology was performed when brady- or tachyarrhythmias were suspected of being responsible for the incidence of faintings. Patients had no clinical major endogenous depression or panic disorder and were all unresponsive to or intolerant of previous therapies. The study was performed according to the guidelines of the institutional committee on human research. All patients gave written informed consent.

**Tilt test protocol.** Patients underwent head-up tilt test between 10 a.m. and 12 a.m. after a 12 h fasting period. After baseline blood pressure and heart rate value measurements, each patient was tilted to 60° for up to 45 min (18). If syncope developed during the tilt, the patient was immediately lowered to the supine position, and the study ended. If no symptoms developed, the test was prolonged for up to 20 min after 5 mg sublingual isosorbide dinitrate (Carvasin, Wyeth, Havant, United Kingdom) administration (19). Blood pressure was recorded by an automatic sphygmomanometer (Criticon Dinamapp) on the right arm while heart rate was monitored by a 12-channel electrocardiogram (Hewlett-Packard Pagewriter XLi, Cupertino, California). A positive head-up tilt test was defined as the provocation of hypotension, bradycardia or both associated with a loss of consciousness that reproduced the patients' clinical episodes (20).

**Previous therapies.** In each case, the patients' traditional therapies were either ineffectual or poorly tolerated. Failure was defined as the clinical recurrence of syncope. Patients had been unresponsive to or intolerant of 75 mg daily of ethylephrine (17 patients), 80 mg daily of propranolol (20 patients), either ethylephrine or propranolol (23 patients), 600 mg daily of aminophylline (4 patients), 0.2 mg daily of fludrocortisone (2 patients), 200 mg daily of dysopiramide (1 patient) and transdermal scopolamine (1 patient). Previous medications were all discontinued before paroxetine or placebo treatment.

**Study protocol.** Each of the sixty-eight patients exhibited a positive response during tilt testing, were given pharmacotherapy and underwent repeat tilt tests. Patients were computer randomized into two follow-up groups and were given either oral paroxetine at 20 mg daily (34 patients) or a placebo tablet (34 patients). Patients, cardiologists and nurses were all blinded to treatment assigned. Paroxetine and placebo tablets were quite similar in appearance and taste, and patients were not able to determine whether they were on paroxetine or placebo. One month after the initiation of therapy, the response to the tilt test was reevaluated in the same laboratory at approximately the same time of day using the same protocol. Recurrence of spontaneous syncope was evaluated by a separate cardiologist over a mean period of 25.4 ± 7.9 months. Each of the sixty-eight patients had a follow-up of at least 24 months (range 24–33).

**Statistical analysis.** The response rate of paroxetine and a placebo was compared by chi square test while other

continuous data were expressed as mean ± SD and compared by Student *t* test. A p value less than 0.05 was considered significant. For multiple statistical comparisons to baseline, a p value less than 0.025 was considered significant.

## RESULTS

**Clinical characteristics (Table 1).** Both groups were comparable in age and ratio of men to women. Duration of syncopal histories, severity (yearly recurrence) of attacks, baseline blood pressure and heart rate values were similar in both groups. During the first tilt test, the placebo group had a mean positive time (to syncope onset) at 29.2 ± 9.7 min, and the paroxetine group, 31.4 ± 11.2 ($p = 0.390$).

**Tilt test repetition.** Acute tilt-induced syncope was observed in 38.2% (13 patients) versus 61.8% (21 patients) in the paroxetine and placebo groups, respectively ($p = 0.001$). A significant increase of mean test duration was observed in the paroxetine group with a mean delay of positive time from 31.4 ± 11.2 min up to 47.8 ± 12.4 min ($p < 0.001$).

**Spontaneous syncope and follow-up.** Before treatments were administered, the placebo group had 7.2 ± 2.1 yearly syncopal episodes, and the paroxetine group had 8.1 ± 3.4 ($p = 0.194$). Spontaneous syncope recurrence during the two year follow-up was 52.9% (18 patients) versus 17.6% (6 patients) in the placebo and paroxetine groups, respectively ($p < 0.0001$). The symptomatic patients in the paroxetine group also reported that their attacks were reduced from 8.1 ± 3.4/year to 5.9 ± 1.7/year ($p = 0.001$), while no significant differences were obtained in the placebo group. No difference in time for recurrence of syncope was observed among the groups. No patients reported feeling worse during follow-up. Only one patient (2.9%) in the paroxetine group asked to be discontinued from the drug for severe recurrent headaches. Two patients in the paroxetine group (transient sexual dysfunction, nausea and diarrhea) and one patient in the placebo group (headache) reported some side effects, but medication was not discontinued. Once a day drug administration was well-accepted in both groups.

## DISCUSSION

Recurrent syncope can be a severely disabling disorder and quality of life deteriorates as a function of the recurrence of episodes.

Not only can these episodes produce physical trauma, but they create a serious psychological discomfort and employment, education and social interactions may be severely restricted.

**Therapy.** Therapy of vasovagal syncope has largely been empiric, based on the mechanism that is currently believed to be the cause of vasovagal faintings. Nevertheless—irrespective of beta-blocking, vagolytic, negative inotropic, mineral corticoid therapy—several patients continue to experience episodes of syncope (refractory syncope). In our series we studied sixty-eight patients with recurrent syncope subjected to previous ineffectual or poorly tolerated 75 mg daily ethylephrine, 80 mg daily propranolol, either ethylephrine or propranolol, 600 mg daily aminophylline, 0.2 mg daily fludrocortisone, 200 mg daily dysopiramide or transdermal scopolamine.

**Serotonin and vasovagal syncope.** The role of central serotonin metabolism in the pathophysiology of vasovagal syncope remains controversial. Several pathophysiologic reactions similar to vasovagal reflex are believed to be mediated by central serotonin level fluctuations (13,14,21,22). The first trials with regard to selective serotonin reuptake inhibition and vasovagal syncope were published by Grubbs et al. (15–17), but these trials were not placebo-controlled. The authors reported clinical success (no syncope) in 68.7% of patients subjected to fluoxetine at 20 mg daily (15) and in 70.6% of those subjected to sertraline at 50 mg daily (16). Nevertheless, severe side effects were reported in 19% and 17.6% in the fluoxetine and sertraline groups, respectively, and patients asked to be discontinued from the drug.

**Paroxetine therapy.** Paroxetine hydrochloride (Seroxat, Smith Kline Beecham Pharmaceuticals, Mayenne, France) is a highly selective serotonin reuptake inhibitor, unlike tricyclic antidepressant agents having poor or no affinity for adrenergic, cholinergic and hystamine receptors. Protein binding is about ninety-five percent. Major metabolites of paroxetine are less powerful serotonin reuptake inhibitors than the parent compound and are not believed to contribute to paroxetine's therapeutic effects. Once a day oral administration allowed steady state plasma levels within 14 days of treatment and was well accepted by patients. In the study paroxetine was found to be an effective therapy for preventing acute tilt-induced (61.8% negative tilt test repetition) and spontaneous syncope (82.4% symptom free) in patients unresponsive to or intolerant of other forms of therapy (refractory syncope). The effects of paroxetine on acute tilt-induced syncope conform to recent reports by Grubb et al. who tested serotonin reuptake inhibition by oral fluoxetine (15) and sertraline (16), but data should be treated with considerable caution given the well-established lack of reproducibility of tilt tests (70% at best) (23–25) and the relatively small number of patients. Paroxetine seems to have major effectiveness in preventing spontaneous syncope as compared with the other serotonin reuptake inhibitors investigated (15–17). Moreover, it was well tolerated, side effects were negligible and only one patient (2.9%) asked to be discontinued from the drug for severe side effects.

The possible mechanism by which serotonin reuptake inhibition improves clinical outcome of patients with refractory neurocardiogenic syncope has been proposed by Grubb et al. since they postulated that, because of their facilitation of nerve transmission, serotonin reuptake inhibitors cause postsynaptic serotonin receptors down regulation

in the brain stem. This down regulation in receptor density is believed to result in a blunted response to rapid shifts in central serotonin levels (15–17).

**Conclusions.** We conclude that paroxetine may represent an effective and well tolerated therapy in patients with recurrent vasovagal syncope who are unresponsive to or intolerant of traditional tilt-guided medication. Major series and longer follow-up periods are needed to resolve the question of the role of selective serotonin reuptake inhibitors in the prophylaxis of refractory neurocardiogenic syncope.

**Reprint requests and correspondence:** Dr. Enrico Di Girolamo, Via F. Molino, 35, 66013 Chieti, Italy. E-mail: barsotti@unich.it.

## REFERENCES

1. Kenny RA, Bayliss J, Ingram A, Sutton R. Head-up tilt: a useful test for investigating unexplained syncope. Lancet 1986;1:1352–4.
2. Mark AL. The Betzold-Jarish reflex revisited: clinical implications of inhibitory reflexes originating in the heart. J Am Coll Cardiol 1983;1:90–102.
3. Van Lieshout JJ, Wieling W, Karemaker JM, Eckberg DL. The vasovagal response. Clin Sci 1991;81:575–86.
4. Abboud FM. Neurocardiogenic syncope. N Engl J Med 1993;328:1117–20.
5. Shalev Y, Gal R, Tchou PJ, et al. Echocardiographic demonstration of decreased left ventricular dimensions and vigorous myocardial contraction during syncope induced by head-up tilt. J Am Coll Cardiol 1991;18:746–53.
6. Rea R, Thames MD. Neural control mechanisms and vasovagal syncope. J Cardiovasc Electrophysiol 1993;4:587–95.
7. Kosinski D, Grubb BP, Temesy-Armos P. Pathophysiological aspects of neurocardiogenic syncope: current concepts and new perspectives. PACE 1995;18:716–24.
8. Chosy JJ, Graham DT. Catecholamines in vasovagal fainting. J Psychosom Res 1965;9:189–94.
9. Wallbridge DR, MacIntyre HE, Gray CE, Oldroyd KG, Rae AP, Cobbe SM. Role of endogenous opioids and catecholamines in vasovagal syncope. Eur Heart J 1996;17:1729–36.
10. Wallbridge DR, MacIntyre HE, Gray CE, Oldroyd KG, Rae AP, Cobbe SM. Increase in plasma beta-endorphines precedes vasodepressor syncope. Br Heart J 1994;71:446–8.
11. Sakuma I, Togashi H, Yoshioka M. N-methyl-L-arginine, an inhibitor of L-arginine-derived nitric oxide synthesis, stimulates renal sympathetic nerve activity in vivo. A role for nitric oxide in the central regulation of sympathetic tone. Circ Res 1992;70:607–11.
12. Shen WK, Hammil SC, Munger TM, et al. Adenosine: potential modulator of vasovagal syncope. J Am Coll Cardiol 1996;28:146–54.
13. Elam RF, Bergmann F, Feuerstein G. The use of antiserotonergic agents for the treatment of acute hemorrhagic shock of cats. Eur J Pharmacol 1985;107:275–8.
14. Kosinski D, Grubb BP. Neurally mediated syncope with an update on indications and usefulness of head-upright tilt table testing and pharmacologic therapy. Curr Opin Cardiol 1994; 9:53–64.
15. Grubb BP, Wolfe DA, Samoil D, Temesy-Armos P, Hahn H, Elliot L. Usefulness of fluoxetine hydrochloride for prevention of resistant upright tilt induced syncope. PACE 1993;16:458–64.
16. Grubb BP, Samoil D, Kosinski D, Kip K, Brewster P. Use of sertraline in the treatment of refractory neurocardiogenic syncope in children and adolescents. J Am Coll Cardiol 1994;24:490–4.
17. Grubb BP, Kosinski D. Preliminary observations on the use of venlafaxine hydrochloride in refractory orthostatic hypotension. J Serotonin Res 1996;6:89–94.
18. Fitzpatrick AP, Theodorakis G, Vardas P, Sutton R. Methodology of head-up tilt testing in patients with unexplained syncope. J Am Coll Cardiol 1991;17:125–30.
19. Raviele A, Menozzi C, Brignole M, et al. Value of head-up tilting test potentiated with sublingual nitroglycerin to assess the origin of unexplained syncope. Am J Cardiol 1995;76: 267–72.
20. Sutton R, Petersen M, Brignole M, Raviele A, Menozzi C, Giani P. A proposed classification for tilt induced vasovagal syncope. Eur J Card Pacing Electrophysiol 1992;3:180–3.
21. Evans RG, Kapoor V, Ludbook J. A CNS serotonergic mechanism in acute central hypovolemia in conscious rabbits. J Cardiovasc Pharmacol 1986;19:1009–17.
22. Kosinski D, Grubb BP, Temesy-Armos P. The use of serotonin reuptake inhibitors in the treatment of neurally mediated cardiovascular disorders. J Serotonin Res 1994;1:85–90.
23. Grubb BP, Wolfe DA, Temesy-Armos P, Hahn H, Elliot L. Reproducibility of head upright tilt table test result in patients with syncope. PACE 1992;15:1477–81.
24. Morillo CA, Klein GJ, Gersh BJ. Can serial tilt testing be used to evaluate therapy in neurally mediated syncope? Am J Cardiol 1996;77:521–2.
25. Raviele A, Gasparini G, Di Pede F, Delise P, Bonso A, Piccolo E. Usefulness of head-up tilt test in evaluating patients with syncope of unknown origin and negative electrophysiologic study. Am J Cardiol 1990;65:1332–7.